Panacea Biotec

Innovation in support of life

IN THE UNITED STATES PATENTS AND TRADEMARKS OFFICE

Application of: JAIN, Rajesh

Serial No.: 10/089,020

Filed On: Mar 27, 2003

For: CONTROLLED RELEASE COMPOSITIONS COMPRISING NIMESULIDE

Group: 1616

Examiner: Pryor Alton Nathaniel

Docket No.: U 013943-5

Commissioner of Patents & Trademarks
Washington, D.C.20231

DECLARATION UNDER 37 CFR 1.132

I, RAJESH JAIN, Ph.D, Joint Managing Director of Panacea Biotec Limited, hereby declare that:

1. I am one of the applicants in the aforesaid application. My C.V. is attached herewith.

2. I would like to bring to the notice of the learned examiner - (i) why there exists a need for a once-a-day composition of nimesulide and why there is a market for an effective and safe controlled-release dosage form of nimesulide globally, that is prepared in a easy and cost effective manner (ii) encouraging *in vivo* efficacy results obtained from the bilayered controlled-release dosage form of nimesulide of the present invention and (iii) the broad acceptance and commercial success of this novel dosage form in the domestic market, in India where it is being sold.

3. Nimesulide (4-nitro-2-phenoxy-methan-sulfanilide) is a potent non steroidal anti-inflammatory drug, presently used in the treatment of painful inflammatory conditions, which also possesses antipyretic activity. Compared to the other non steroidal anti-inflammatory drugs, Nimesulide has a better therapeutic ratio, low acute gastrotoxicity and generally good tolerability with no reported cardiovascular adverse effects. Nimesulide is chemically different from other drugs in this class because of the presence of sulfonamide moiety. Nimesulide has exhibited potency similar to or greater than indomethacin, diclofenac, piroxicam and ibuprofen in animal models. Many published articles report that nimesulide is an effective NSAID with relatively favorable safety profile for the treatment of osteoarthritis and non-rheumatoid musculoskeletal conditions[1]. Nimesulide is different from Naproxen, nimesulide being a selective Cox-2 inhibitor, which makes it more tolerable and safe having reduced to no gastro-intestinal side effects, while Naproxen is a non-selective Cox inhibitor, its acts on both Cox-1 and Cox-2 receptors and thus leads to gastro-intestinal toxicity like ulceration, bleeding, which makes it unacceptable. Safety profile of nimesulide has been demonstrated by many published articles which are enclosed herewith for your kind perusal. Brief on the same is given below:

(i) Denis Riendau et al; discloses the comparative study of COX-1 inhibitory properties of NSAIDs and selective COX-2 inhibitors. It reveals that the selective COX-2 inhibitors possess anti-inflammatory effects with an improved gastro-intestinal tolerability compared with conventional NSAIDs affecting both COX-1 and COX-2[2].

(ii) Shah, A.A. et al; reveals that nimesulide has preferential selectivity for COX-2 over COX-1 *in-vivo* as full therapeutic doses and induces less gastrointestinal damages than that seen with naproxen in the short term[3].

(iii) Sheikh Arshad Saeed et al reported the anti-ischemic effect of nimesulide. In this study, it has been demonstrated that the nimesulide has significant improvement in the coronary perfusion rate which strongly suggest that coronary vasodilation occurs through endothelial dependant NO formation. There is evidence that COX-2 may be a source of oxygen radical itself and therefore, inhibition of this enzyme activity by nimesulide may reduce oxidative stress[4].

(iv) It has been further reviewed by Rainsford K.D. that the nimesulide has relatively low occurrence of gastro-intestinal side effects which is related to its low propensity to inhibit the physiologically important COX-1 in the GI mucosa and important physiochemical properties as well as inhibiting of mast cell derived histamine and acid secretion in the stomach. In contrast with coxib, nimesulide has not been found to have appreciable cardiovascular toxicity[5].

4. At the time of development of this invention, nimesulide was available as oral immediate release dosage form to be administered up to 100 to 200 mg twice daily. I realized that for treatment of chronic diseases like arthritis the twice-daily dosing regimen is quite difficult to comply with. There was an impending need to develop a once-a-day composition to significantly increase the dosing convenience and patient compliance. There was also a need to develop a composition which will provide some part of the drug, nimesulide, as an immediate release pulse and release the remaining part of the drug as a constant release for extended period of time, thus providing a better efficacy in treatment of NSAID indicated disorders. Prior arts had suggested methods which were difficult to manufacture and were not cost effective, hence there was a need to develop the formulation in a very simple and cost effective manner.

5. This lead to the development of the once-a-day controlled-release tablet composition consisting of a single unit fast release layer and a single unit extended release layer (essentially bilayered tablet) comprising nimesulide as an active agent in both the layers, extended release layer further comprising rate controlling material as claimed. Surprisingly this formulation has an increased residence time in the desired site of absorption such as stomach and proximal part of small intestine, which makes it very advantageous over all prior arts particularly in terms of providing a better absorption of nimesulide and thus its efficacy. The said dosage form of nimesulide eliminates the absorption of nimesulide from distal part of small intestine and large intestine which lead to the loss of bioavailability. This rendered a novel feature to this invention.

6. A similar controlled-release once-a-day composition of nimesulide as described in our present invention in Example 10, has been studied *in vivo* against conventional

nimesulide dosage form i.e. Aulin 100mg. Details on the test that were conducted and the results obtained have been discussed in Annexture-1

7. The said composition of nimesulide was also tested *in vivo* against other NSAIDs (Diclofenac- SR 100 mg) to show comparative efficacy and safety and was found to be very comparable. Efficacy and safety data of Nimesulide Extended Release Tablet 200mg have been demonstrated in Annexture-2

8. I believe that the said composition of nimesulide has broader acceptance and success in the market place. Herein applicant provides you information in Anexture-3 (at best available to me) about-

   (i) Total population for osteoarthritis patient globally
   (ii) Available treatment for osteoarthritis, an inflammation disorder
   (iii) Features of the claimed invention which render the composition as claimed to be highly effective and safe
   (iv) Sales data of claimed product

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Signed this 20th day of April, 2009

Signature:----------
(RAJESH JAIN, Ph.D)

Panacea Biotec
Innovation in support of life

Personal information Sheet

Name : **Rajesh Jain**

Designation : **Joint Managing Director**

Qualification :
1. **Graduation in Science from Delhi University**
2. **Post Graduate Diploma in Business Management**
3. **Advance Research Diploma in Market Research**
4. **PhD in Management**

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E-mail: rajeshjain@panaceabiotec.com

Current Profile

Dr. Jain serves a Joint Managing Director for Panacea Biotec Ltd. Providing the strategic, visionary leadership, management and guidance, he is responsible for marketing and research and development. Dr. Jain is also on the Board of Directors. His broad expanse of experience and qualifications in biotechnology enables him to efficiently handle his divergent duties. Sharing ideas and techniques in an enthusiastic and persuasive manner, he provides the most practical and comprehensive solutions to keep the company out in front of the industry. Utilizing outstanding analytical skills and an exceptional knowledge of science, he fortifies policies and strategies that contribute to the Company's overall record of success and maintain its superlative legacy of excellence.

: 2 :

Dr. Rajesh Jain has been actively involved in the development, introduction and commercialization of a novel dosage form of Nimesulide product in India and has also been actively involved in other innovative projects including Cyclosporine, Mycophenolate Mofetil and others.

He occupies various prominent positions at different academic and Government bodies viz;

1. **Chairman** - BiotechnologySub-Committee, Confederation of Indian Industry (CII) Northern Region.
2. **Vice President** - Association of Biotechnology Led Enterprises (ABLE)

Northern Region

3. **Member** - Pharmaceuticals and Biotechnology Committee of Federation of Indian Chambers of Commerce Industry Federation (FICCI).

4. **Member** - Joint Task Force CII, Govt. of Uttaranchal

5. **Member** - Vaccine Production Board, Govt. of India, DGHS, New Delhi.

6. **Member** – Advisory Committee of the Biotechnology Teaching Programme, Centre for Biotechnology Jawaharlal Nehru University – Delhi.

7. **Member** – Regional Advisory / Public Grievances Committee, Central Excise Collectorate, Jaipur.

8. **Member** - Information Technology Department, Biotech Industry

9. **Partner** - Global Alliance for Vaccines and Immunization (GAVI Board-member for Developing Country Vaccine Manufacturers WHO).

10. **Consultant to WHO** - Development of Polio Vaccine (for 2 years).

11. **Publications-** WTO: with reference to Indian Pharmaceutical Industry, *Business Perspectives, Volume 4, Number 1 January-June, 2002*

Family Business – Roots of Failure: A review
Business Perspectives, Volume 5, Number 1 January-June, 2003

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References

1. S.K. Kulkarni; "On the safety of nimesulide, a preferential COX-2 inhibitor"; *Current Science*; Vol. 83, No. 12; 1442-3 (Dec 2002).
2. Denis Riendeau et al; "Comparison of the cyclooxygenase-1 inhibitory properties of nonsteroidal anti-inflammatory drugs (NSAIDs) and selectiveCOX-2 inhibitors, using sensitive microsomal and platelet assays"; *Can. J. Physiol. Pharmacol.;* 75: 1088-1095 (1997)
3. A A shah et al; "Selective inhibition of COX-2 in humans is associated with less gastrointestinal injury: a comparison of nimesulide and naproxen"; *Gut;* 48: 339-346; (2001)
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5. K.D. Rainsford "Current status of the therapeutic uses and action of the preferential cyclo-oxygenase-2 NSAID, nimesulide"; *Inflammopharmacology;* 14; 120-137: (2006)
6. The Pain Market Outlook to 2011. Business Insights. 2006.
7. Singh, G et al. Prevalence of Cardiovascular Disease Risk Factors Among US Adults With Self-Reported Osteoarthritis: Data from the Third National Health and Nutrition Examination Survey. The American Journal of Managed Care. Vol. 8, No. 15, Sup.
8. Chou R, Helfand M, Peterson K, et al. Comparative Effectiveness and Safety of Analgesics for Osteoarthritis. Comparative Effectiveness Review No. 4. Prepared by the Oregon Evidence-based Practice Center. Prepared for the Agency for Healthcare Research and Quality. September 2006. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed on September 12, 2007.

ANNEXTURE- 1

Two pivotal studies were conducted to characterize the pharmacokinetics of Nimesulide ER 200 mg tablets. The studies consisted of a (i) single-dose 3-arm fasting/fed study and a (ii) multiple-dose steady-state study

(1) Relative bioavailability of Nimesulide Extended Release Tablets 200 mg under fasting and Fed condition [Single-dose 3-arm fasting/fed study]

A randomized, open label, three-treatment, three-period, three-sequence, single dose, crossover, comparative bioavailability study, to assess the relative bioavailability of Nimesulide Extended Release (ER) Tablet 200 mg of Panacea Biotec Limited, India, Willgo® (under fasting and fed conditions) (similar in composition to that given in our present invention in Example 10) with Aulin® (Nimesulide 100 mg) Tablets of CSC Pharmaceuticals, Austria (under fasting condition) was carried out in healthy human adult male subjects.

A total of 36 healthy, adult male subjects aged between 18 - 50 years, having a body mass index (BMI) between 18 and 25 were enrolled for the study and housed for at least 37 hours. The study was conducted in three periods. In each period, subjects were dosed with one of the 3 study treatments: Treatment A: One tablet of Nimesulide ER 200 mg under fasting conditions, Treatment B: One tablet of Nimesulide ER 200 mg under fed conditions, Treatment C: Two tablets of Aulin® (Nimesulide 100 mg) under fasting conditions.

Sampling was done up to 24.0 hours such that the plasma concentration could be measured for adequately profiling the pharmacokinetics of the product. Study periods were separated by a washout period of 7 days for complete elimination of the product substance.

Summary of Pharmacokinetic data for Nimesulide ER 200 mg Tablet (Single dose Study)
Table 1

Parameters	*Single Dose study*		
	Test (Fasting)	*Test (Fed)*	*Reference (Fasting)*
AUC_{0-t} (μg.h/ml)	48.6004	93.6634	98.7289
$AUC_{0-\infty}$ (μg.h/ml)	51.0648	98.7918	102.9535
C_{max} (μg/ml)	5.6954	10.7552	12.9410
T_{max} (h)	2.98	5.12	2.38
$t_{1/2}$ (h)	4.04	4.15	3.97
K_{el} $(h)^{-1}$	0.1870	0.1837	0.1947
AUC_{0-t}/ $AUC_{0-\infty}$	0.9565	0.9556	0.9685

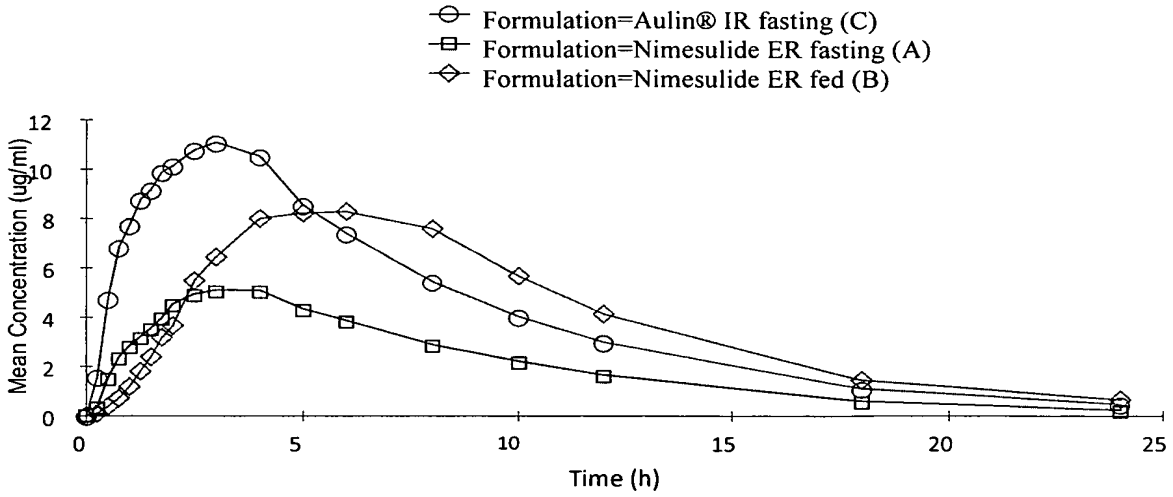


Fig. 1: Linear Plot of Mean Plasma Nimesulide Concentrations versus Time Profiles in Healthy Human Adult Male Subjects

Conclusion: As seen in Figure 1 food significantly increases the absorption of nimesulide from the extended release composition of the present invention and is bioequivalent to Aulin. Both test and reference formulations were found to be well tolerated in this study.

(2) A randomized, open label, two- treatment, two-period, two-sequence, multiple-dose, crossover, relative bioavailability study of Nimesulide Extended Release Tablets 200 mg Willgo® [Multiple-dose steady-state study].

A randomized, open label, two-treatment, two-period, two-sequence, multiple-dose, crossover, relative bioavailability study of Nimesulide Extended Release Tablet 200 mg of Panacea Biotec Limited, India with Aulin® (Nimesulide 100 mg) tablets (administered twice daily) of CSC Pharmaceuticals Austria, was conducted in healthy human adult male subjects, under fed condition.

A total of 36 healthy, adult male subjects of either sex aged between 18-50 years (inclusive) having a body mass index (BMI) between 18 and 25 were enrolled for the study. The subjects were dosed as determined by the randomization schedule.

(ANNEXTURE- 1 Contd.....)

There was a washout period of 8 days following administration of test product and 7½ days following administration of reference products between the dosings.

Summary of Pharmacokinetic data for Nimesulide ER 200 mg Tablet (Multiple dose Study)
Table 2

Parameters	*Multiple Dose study under fed condition*	
	Test - A	*Reference - B*
C_{min} (µg/ml)	0.5948	1.6482
C_{avg} (µg/ml)	4.0494	4.5142
C_{max} (µg/ml)	11.0428	8.5409
$AUC_{0-\tau})_{ss}$ (µg.h/ml)	97.1846	108.3398
%PTF	278.64	165.32
Swing	3424.78	685.88

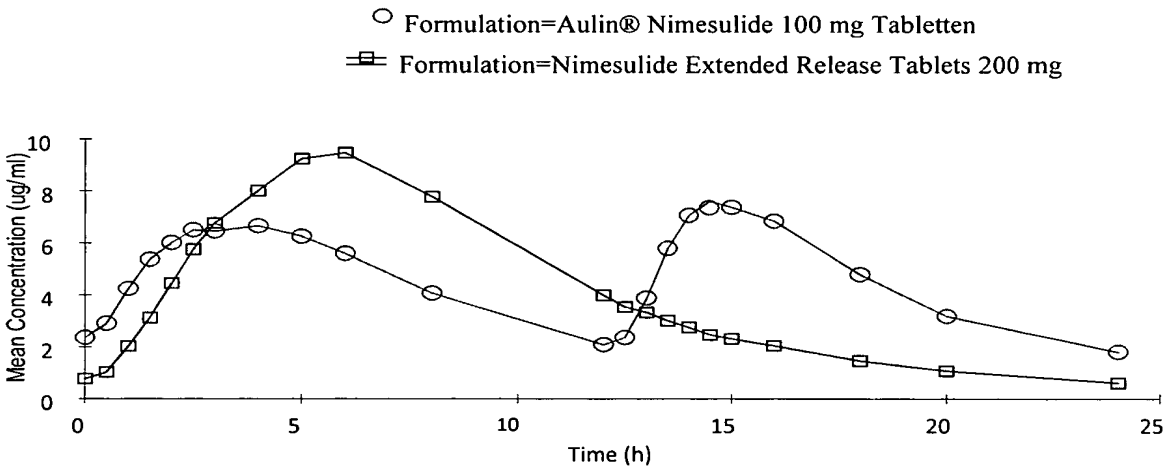


Fig. 2: Linear Plot of Mean Plasma Nimesulide Concentrations versus Time Profiles in Healthy Human Adult Male Subjects

Conclusion: The estimated relative extent of absorption for a steady-state dose of nimesulide ER based on $(AUC_{0-\tau})_{ss}$ is ~90% that for Aulin. Both the test and reference formulations were found to be well tolerated this study.

Conclusions from Pharmacokinetic Studies

Nimesulide Extended Release Tablets 200 mg have acceptable tolerability results as it does not exceed the exposure and peak plasma concentration compared to the conventional release 100 mg tablets taken twice daily for chronic pain management.

ANNEXTURE-2

Purpose: To compare the efficacy and safety of Nimesulide ER 200 mg (Willgo®) with Diclofenac SR 100 mg (Voveran®SR) in patients with osteoarthritis knee.

Study design: Open label, randomized, active-comparative controlled, multicentre, non-inferiority trial.

Methods: 262 patients aged > 45 years diagnosed to have osteoarthritis (OA) of the knee were randomized (1:1) in this multicentre study across India. Patients were allocated to receive either Willgo® (n = 131) or Voveran SR® (n = 131) tablet as per computer generated randomization once daily for a study treatment period of 30 days. Protocol assessment visits were on days 15 and 30. Primary efficacy endpoint was evaluated using VAS (Visual Analogue Scale) of 10 cm for pain at baseline, day 1 (multiple time points), day 15 and day 30. WOMAC OA index 3.1 was evaluated at enrollment and end of therapy. Nimesulide ER was to be considered non-inferior if the lower bound of 95% confidence interval (CI) for the treatment difference (Test - Reference) in mean VAS reduction for pain was less than 1 cm (clinically acceptable significant difference). Safety was evaluated by analyzing all reported clinical adverse events.

The study was conducted by using the standard tool available wherein primary efficacy endpoint was evaluated using VAS (Visual Analogue Scale) of 10 cm for pain and WOMAC OA index 3.1 (Western Ontario and McMaster Universities, osteoarthritis index) for pain + physical function was evaluated at enrollment and end of therapy.

Efficacy Criteria:

1) Primary endpoint
   a) Measurement of pain using a 10 cm VAS (Visual Analogue Scale)
2) Secondary endpoints
   a) Measurement of pain and function using WOMAC OA index
   b) Investigator global assessment of efficacy and tolerability using a 4-point scale
   c) Patient global assessment of efficacy and tolerability using a 4-point scale

Safety Criteria:

- All volunteered and observed adverse events (AEs)

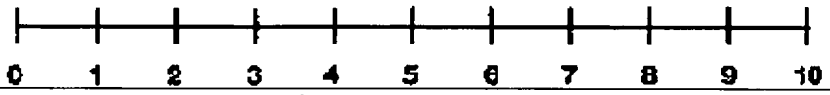
(ANNEXTURE- 2 Contd.....)

The WOMAC™ (Western Ontario and McMaster Universities) OA Index is used to assess subjects with OA knee or hip using 24 parameters. It can be used to monitor the course of the disease or to determine the effectiveness of medications. Parameters assessed as per the latest version of the instrument (WOMAC™ 3.1 Index) and scoring and interpreting the response to parameters on 10 cm VAS are given below:

Table 3: Parameters for WOMAC™ 3.1 Index

Pain (Pain + Stiffness)	Physical Function
Pain: (1) Walking on flat surface (2) Going up or down stairs (3) At night while in bed (4) Sitting or lying (5) Standing upright *Stiffness*: (1) After first wakening in the morning (2) After sitting, lying or resting later in the day	(1) Descending stairs (2) Ascending stairs (3) Rising from sitting (4) Standing (5) Bending to floor (6) Walking on flat (7) Getting in/out of car (8) Going shopping (9) Putting on socks/stockings (10) Rising from bed (11) Taking off socks/stockings (12) Lying in bed (13) Getting in/out of bath (14) Sitting (15) Going on/off toilet (16) Heavy domestic duties (17) Light domestic duties

- ***Table 4 : Scoring and Interpretation of Response to parameters on 10 cm VAS***



Total score = SUM

Average score = (Total score) / (number of items)

Interpretation

Minimum average score: 0 (No pain)

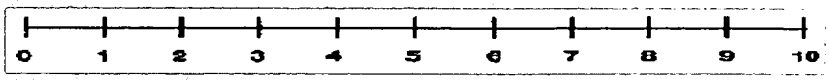
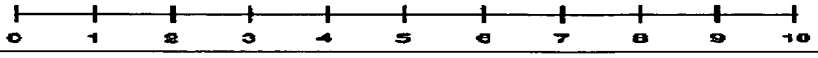
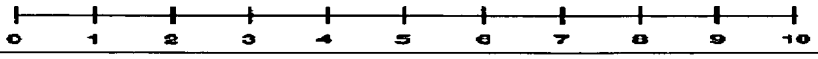
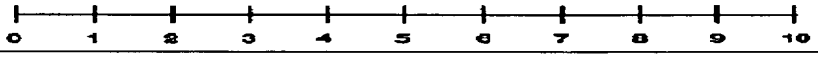
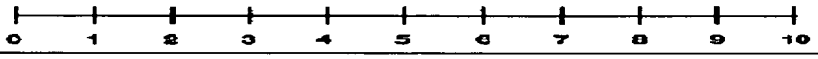
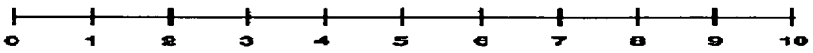
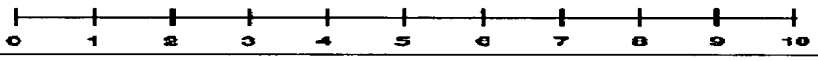
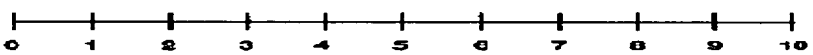
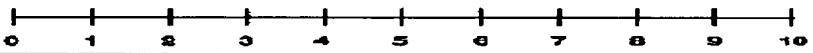
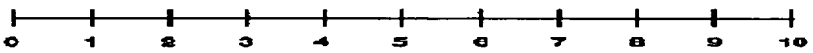
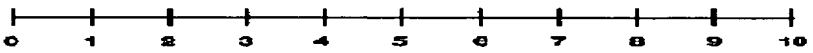
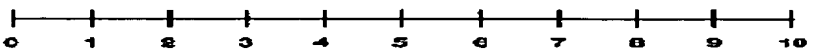
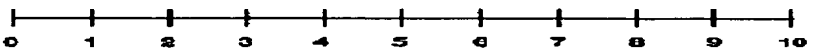
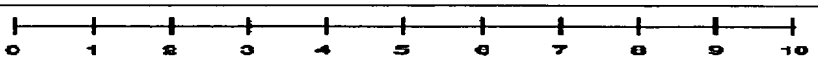
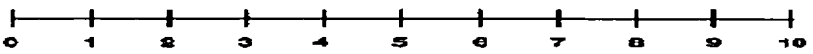
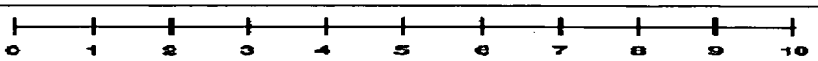
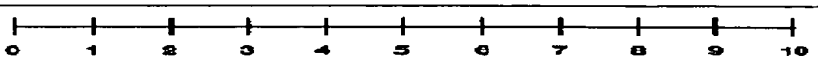
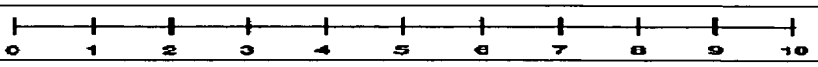
Maximum average score: 10 (Worst pain)

For further clarity please refer to patient diary card (sample in Table 5 below) used in the clinical studies to capture data for patients self rated assessment of pain and function using WOMAC OA index

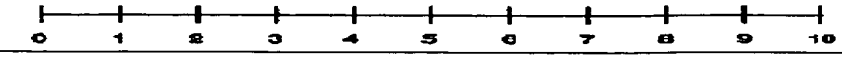
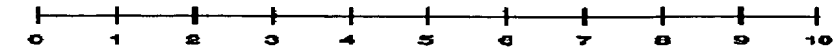
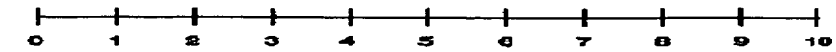
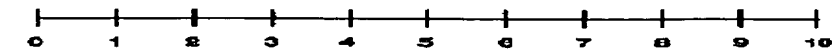
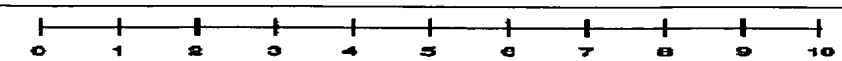
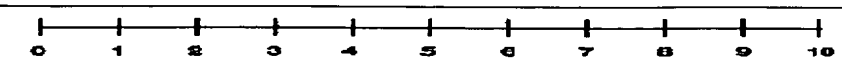
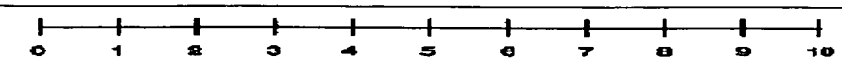
(ANNEXTURE- 2 Contd.....)

(pain + physical function number of variables (7+17=24), scored 0-10 cm on VAS where 0 = No pain and 10 = Worst pain) using WOMAC™ OA Index (Version 3.1).

Table 5: PATIENT DIARY CARD

Patients Self Rated Assessment on WOMAC using Visual Analogue Scale		
Self rated assessment to be completed by the patient based on their experience while performing respective activity		
0-10 cm VAS	 0 = Best ever & 10 = Worst ever	
Pain		
(1) Walking on flat surface		
(2) Going up or down stairs		
(3) At night while in bed		
(4) Sitting or lying		
(5) Standing upright		
Stiffness		
(1) After first wakening in the		
(2) After sitting, lying or resting later in the day		
Physical Function		
(1) Descending stairs		
(2) Ascending stairs		
(3) Rising from sitting		
(4) Standing		
(5) Bending to floor		
(6) Walking on flat		
(7) Getting in or out of car		
(8) Going shopping		
(9) Putting on socks / stockings		
(10) Rising from bed		

(ANNEXTURE-2 Contd..)

(11) Taking off socks / stockings		
(12) Lying in bed		
(13) Getting in/out of bath		
(14) Sitting		
(15) Going on/off toilet		
(16) Heavy domestic duties		
(17) Light domestic duties		
→ **Patient's self rated global assessment of disease using 10 cm VAS including non-signal joints**		

Results:

Efficacy

Non-Inferiority Primary Efficacy Analysis

Lower 95% CI of difference between treatment groups in mean change from baseline should be within 1 using a patient self-rated 10 cm VAS scale for pain.

The treatment difference, that is, Test - Reference (Willgo® - Voveran® SR) in mean VAS reduction, along with the associated 95% CI (defined by the lower limit (LL) and the upper limit (UL)), is shown in Table 6, using mITT study population.

Table 6: Difference in mean VAS reduction, with 95% CI

					Difference in mean VAS reduction (Nimesulide ER – Diclofenac SR)		
						95 % CI	
Product	**Nimesulide ER**		**Diclofenac SR**		**NIM - DIC**	**LL**	**UL**
	N		N				
Mean VAS reduction	119	5.46	119	4.87	0.59	-0.091	1.284

(ANNEXTURE- 2 Contd.....)

The interpretation of above table 6 is that - In mITT analysis mean VAS reduction was 5.46 for Nimesulide ER (Willgo®) and 4.87 for Diclofenac SR (Voveran® SR). The treatment difference (Nimesulide ER - Diclofenac SR) in mean VAS reduction was 0.59, with a lower bound 95% CI of –0.091, which was within the pre-specified non-inferiority margin of 1 cm.

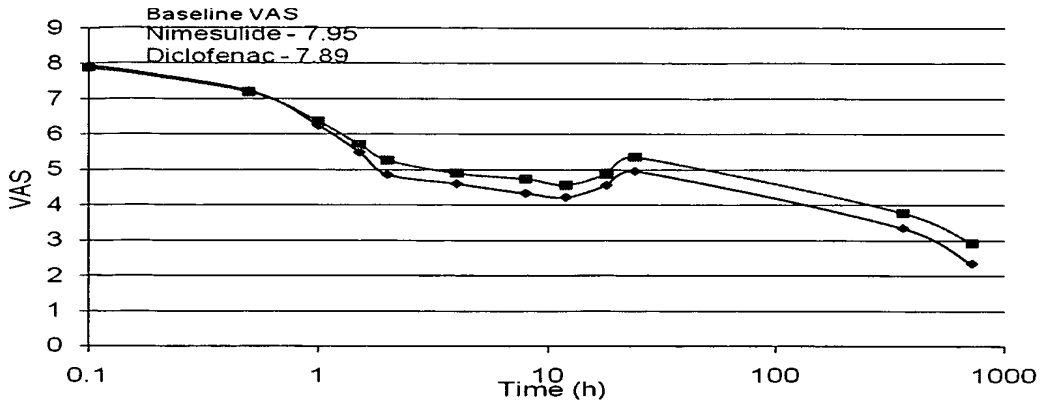
Additional Efficacy Analysis: In both treatment arms statistically significant decrease in pain was observed from baseline to 30 min after treatment, with additional decrease occurring at subsequent hours on Day 1 and during observations made on Day 15 and Day 30. On Day 1, maximum pain relief was achieved after 12 h in both arms (45% and 41% reduction from baseline for Willgo and Voveran SR, respectively). The VAS scores obtained in the Willgo treatment group were lower than that in the Voveran SR treatment group at every assessment. Statistically significant lower scores were observed at 8 h (Day 1) and Day 30 for Willgo group as compared to the Voveran SR group ($p<0.05$).

Table 7: VAS Score

Time Points	VAS Score	
	Nimesulide ER	**Diclofenac SR**
Baseline	7.95 ± 1.36	7.89 ± 1.46
0.5 hr	7.22 ± 1.69	7.19 ± 1.68
1 hr	6.25 ± 1.77	6.36 ± 1.84
1.5 hr	5.50 ± 1.92	5.71 ± 1.90
2 hr	4.87 ± 1.81	5.27 ± 1.88
4 hr	4.61 ± 1.56	4.90 ± 1.65
8 hr	4.34 ± 1.37*	4.74 ± 1.55
12 hr	4.23 ± 1.56	4.57 ± 1.55
18 hr	4.57 ± 1.43	4.89 ± 1.38
24 hr	4.97 ± 1.64	5.36 ± 1.51
Day 15	3.36 ± 1.77	3.78 ± 1.68
Day 30	2.35 ± 1.91*	2.93 ± 2.02

*$p<0.05$

Figure 3: VAS Score



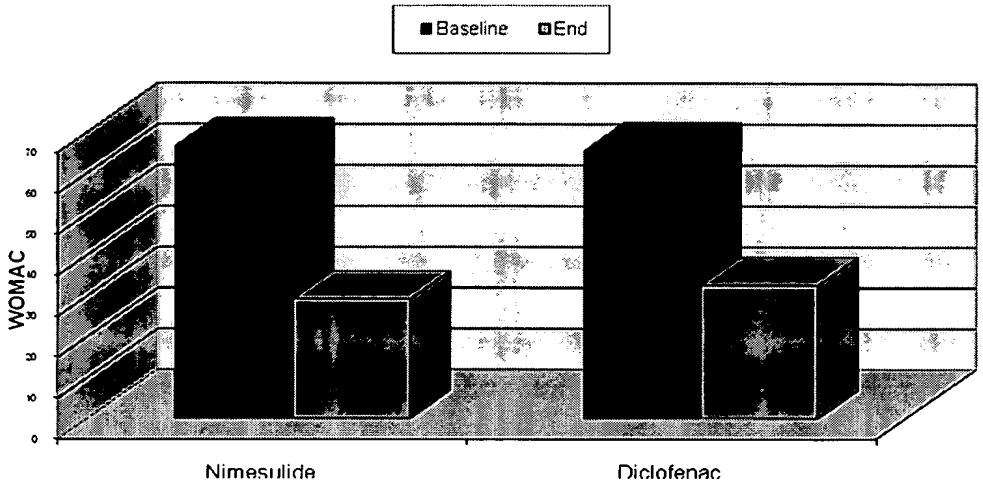
Conclusion: Nimesulide Extended Release Tablets 200 mg OD is non-inferior to Voveran SR (Diclofenac sodium) 100 mg OD in mean VAS Reduction for pain at 1 month in osteoarthritis knee. The novel ER product is expected to be more patient compliant alternative to the existing IR product.

Table 8: WOMAC index

Time points	WOMAC score	
	Nimesulide ER N=112	**Diclofenac SR N=110**
Baseline	66.57	65.58
End of therapy (Day 30)	29.22	32.58

(ANNEXTURE- 2 Contd.....)

Figure 4: WOMAC Index



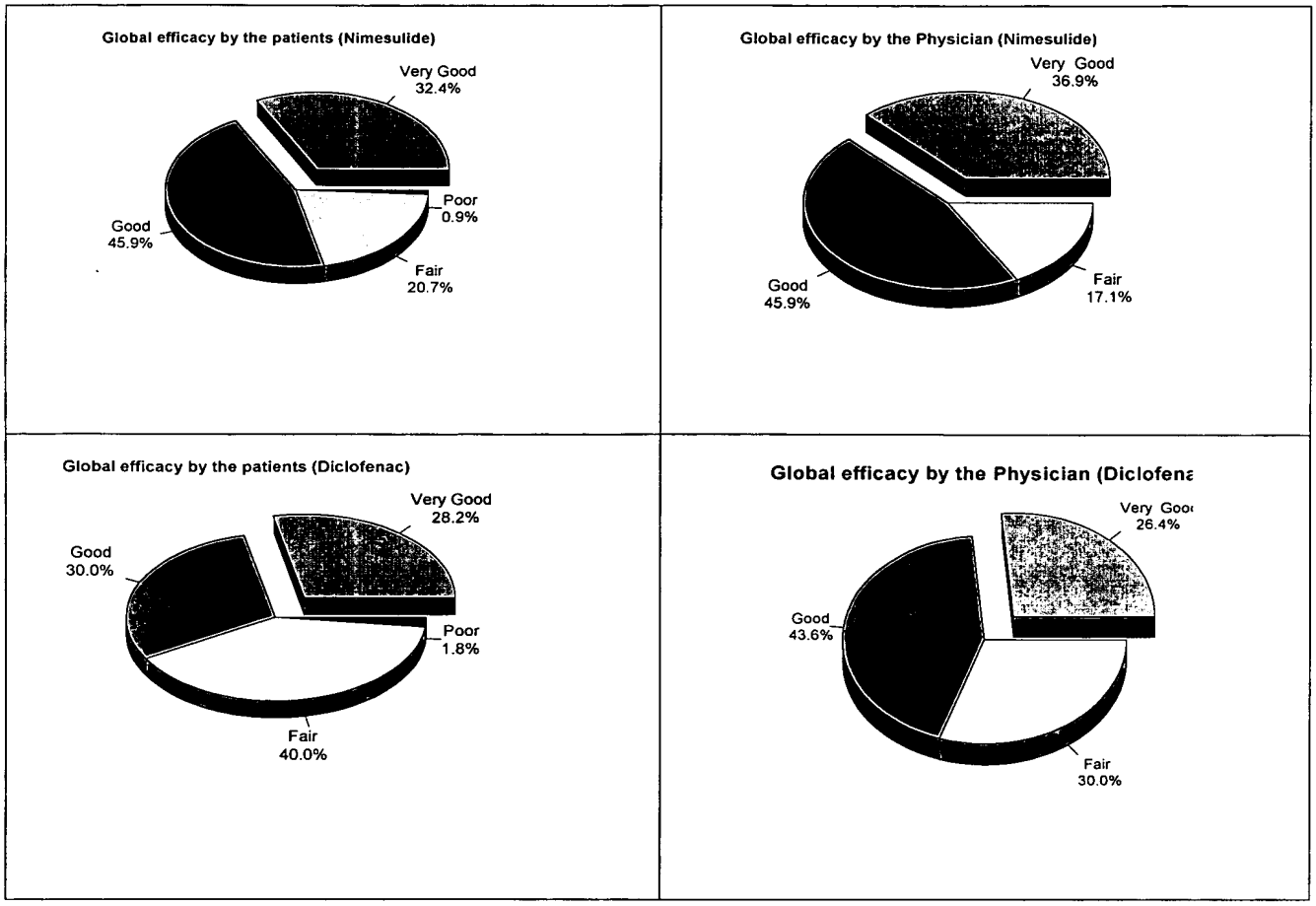
Conclusion: No statistically significant difference was observed in the WOMAC scores obtained in the two groups at baseline, as seen in Table 8 and Figure 4 (66.57 for Willgo and 65.58 for Voveran SR). Both groups exhibited a statistically significant decrease in WOMAC scores at the end of the therapy. The Willgo group had a favorable reduction over baseline (56.1%) as did Voveran SR (50.3%).

Global assessment of efficacy and Global tolerability by the Patient and Physician was evaluated on a 4-point scale

Global Efficacy: At day 30, both investigator and patient expressed their global assessment of efficacy of the treatment (Improvement as very good >75%, good >50% to 75%, Fair 25% to 50%, poor < 25%). According to investigator, positive (very good or good) outcomes were observed in 82.88% of the patients treated with Willgo compared with 70% of those treated with Voveran SR. Similar outcome were expressed by patients: 78.38% of the Willgo treated patients and 58.18% of the Voveran SR treated patients recorded a positive outcome as seen in Table 9 below.

(ANNEXTURE- 2 Contd…..)

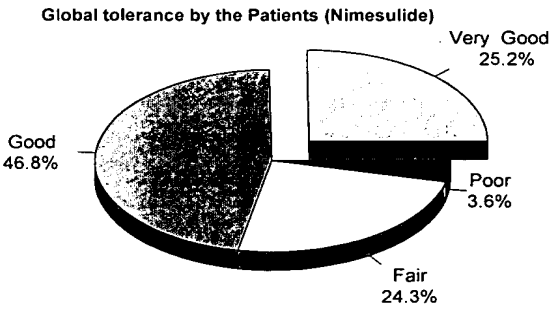
Table 9:

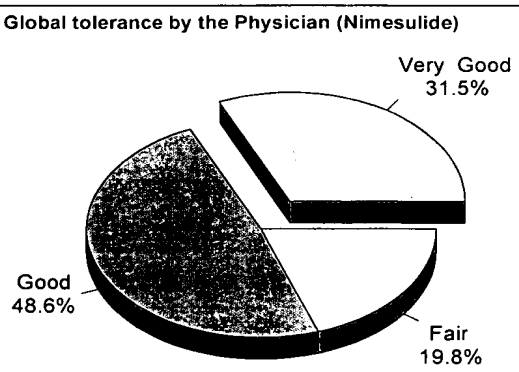


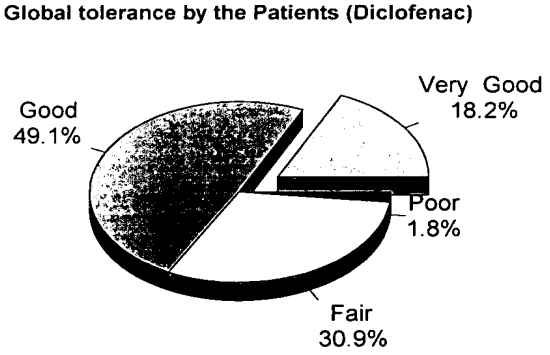
(ANNEXTURE- 2 Contd.....)

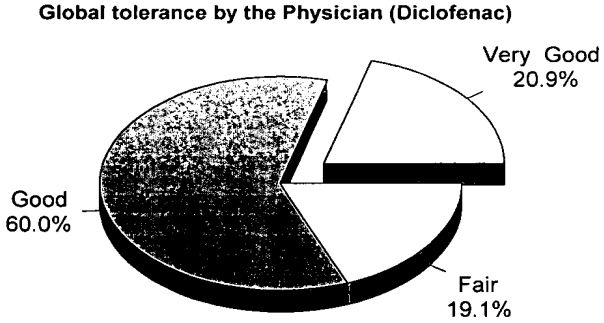
Global Tolerability: In tolerability assessment, investigator reported positive outcome (very good or good) in 80.18% patients in the Willgo group compared to 80.91% patients in the Voveran SR group. Positive outcome was reported by 72.08% patients in the Willgo group compared to 67.27% patients in the Voveran SR group as seen in Table 10 below.

Table 10:









Conclusion: Both the study treatment produced significant improvement in global assessment of efficacy and tolerability as assessed by the investigators and the patients.

Pharmacovigilance study on Nimesulide ER 200 mg (Willgo®)

The pharmacovigilance programme for Willgo® (Nimesulide Extended Release Tablets 200 mg) was conducted using the methodology similar to prescription-event monitoring (PEM).

Objectives: The objectives of this pharmacovigilance program were:

1. To capture adverse drug reactions (ADRs) suspected to be caused by Willgo®.
2. To gather data regarding prescription of Willgo®, by prescribers to form denominator for safety data collected.
3. To archive the safety information to develop a comprehensive safety database for Willgo®.
4. To compare the incidence rate of Willgo® with Nimesulide.

Methodology: This program had a methodology similar to prescription event monitoring. Data for this program were gathered from 1826 prescribers (physicians, orthopedists, surgeons, dentists, etc.) who participated in the Willgo® Pharmacovigilance program from 161 cities all over India. The participation of prescribers was voluntary with no incentives attached.

Each of the participating prescribers were supplied with a pharmacovigilance booklet containing a prescription log sheet, suspected ADR reporting forms, a project flow-chart, a Willgo® package insert and information about pharmacovigilance program. Self-addressed Business Reply Envelopes were provided to the prescribers, and a monthly reminder email was send to all prescribers participating in this pharmacovigilance program.

The prescribers sent back the data in the form of prescription log sheets and suspected ADR forms. A provision was kept for adding any ADR report spontaneously generated (by a prescriber not participating in this pharmacovigilance program) and sent directly to the sponsor. The prescription log sheets and ADR forms as received were entered in the database.

Prescription event monitoring program to capture adverse drug reactions suspected to be caused by Nimesulide ER (Willgo®) involving a total of 112,730 patients who were prescribed Willgo.

The total exposure was 1,321,449 patient days and the mean exposure was 11.72 ± 8.47 days. While analyzing the data, it was assumed that all the patients being prescribed Willgo® would be exposed to it for the said period; and those patients who did not report to the prescriber did not have any adverse reaction. For calculating the number of patients, patients with multiple prescriptions refill, etc. were counted as one, and duplicated entries were excluded. Any adverse reaction report related to the use of Willgo®, also, is included in the numerator, whether or not the reporter was a prescriber participating in this Pharmacovigilance program. The denominator for the drug usage was obtained by using number of prescriptions (~exposure days).

Results:

A comparison for the rate of occurrence of suspected ADRs expressed in standard category of frequency, i.e. very common (>1/10); common (frequent) (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000) and very rare (<1/10,000) according to summary of product characteristics (SPC) is shown in Table 11. In the EMEA SPC of "Nimesulide" 100 mg tablet[23], the listing of undesirable effects is based on data from controlled clinical trials (approximately 7,800 patients) and from post marketing surveillance.

Table 11: Comparison of the frequency of suspected ADRs

Body system/ADR term	Present Study	EMEA SPC of "Nimesulide"
Blood disorders		
Anaemia	Not reported	Rare
Eosinophilia	Not reported	Rare
Thrombocytopenia	Not reported	Very rare
Pancytopenia	Not reported	Very rare
Purpura	Not reported	Very rare
Immune system disorders		
Hypersensitivity	Not reported	Rare
Anaphylaxis	Not reported	Very rare
Metabolism and nutrition disorders		
Hyperkalaemia	Not reported	Rare
Psychiatric disorders		
Anxiety	Not reported	Rare
Nervousness	Not reported	Rare
Nightmare	Not reported	Rare
Nervous system disorders		

Dizziness	Very rare	Uncommon
Headache	Not reported	Very rare
Somnolence	Very rare	Very rare
Encephalopathy (Reye's syndrome)	Not reported	Very rare
Eye disorders		
Vision blurred	Not reported	Rare
Visual disturbance	Not reported	Very rare
Ear and labyrinth disorders		
Vertigo	Very rare	Very rare
Cardiac disorders Tachycardia	Not reported	Rare
Vascular disorders		
Hypertension	Not reported	Uncommon
Haemorrhage	Very Rare	Rare
Blood pressure fluctuation	Not reported	Rare
Hot flushes	Not reported	Rare
Respiratory disorders		
Dyspnoea	Not reported	Uncommon
Asthma	Not reported	Very rare
Bronchospasm	Not reported	Very rare
Gastrointestinal disorders		
Diarrhoea	Very rare	Common
Nausea	Very rare	Common
Vomiting	Very rare	Common
Constipation	Not reported	Uncommon
Flatulence	Very rare	Uncommon
Gastritis	Very rare	Uncommon
Abdominal pain	Very rare	Very rare
Dyspepsia	Very rare	Very rare
Stomatitis	Very rare	Very rare
Melaena	Not reported	Very rare
Gastrointestinal bleeding	Very rare	Very rare
Duodenal ulcer and perforation	Not reported	Very rare
Gastric ulcer and perforation	Not reported	Very rare
Hepato-biliary disorders		
Hepatitis	Not reported	Very rare
Fulminant hepatitis (including fatal cases)	Not reported	Very rare
Jaundice	Not reported	Very rare
Cholestasis	Not reported	Very rare
Skin and subcutaneous tissue disorders		
Pruritis		
Rash	Very rare	Uncommon
Increased sweating	Very rare	Uncommon
Erythema	Not reported	Uncommon
Dermatitis	Not reported	Rare
Urticaria	Not reported	Rare

Angioneurotic oedema	Very rare	Very rare
Face oedema	Not reported	Very rare
Erythema multiforme	Very rare	Very rare
Stevens Johnson syndrome	Not reported	Very rare
Toxic epidermal necrolysis	Not reported	Very rare
	Not reported	Very rare
Renal and urinary disorders		
Dysuria	Not reported	Rare
Haematuria	Not reported	Rare
Urinary retention	Not reported	Rare
Renal failure	Not reported	Very rare
Oliguria	Not reported	Very rare
Interstitial nephritis	Not reported	Very rare
General disorder		
Oedema	Rare	Uncommon
Malaise	Not reported	Rare
Asthenia	Not reported	Rare
Hypothermia	Not reported	Very rare
Investigations		
Hepatic Enzymes increased	Not reported	Common

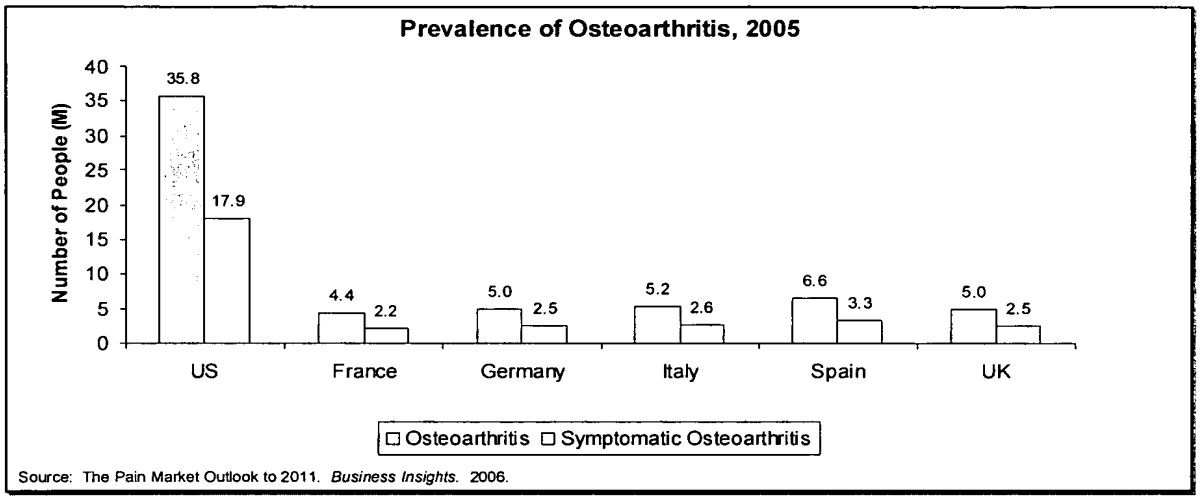
Conclusion: The results of the current study, coupled with the results of previous studies, demonstrate that Nimesulide Extended Release Tablet 200 mg is well tolerated and safe for treatment of osteoarthritis, rheumatoid arthritis and other painful inflammatory conditions.

No major adverse cardiovascular event has been reported in any of the above clinical trials and prescription event monitoring program.

ANNEXTURE-3

Osteoarthritis (OA) is a progressive bone and joint disorder that can lead to severe joint pain and decreased patient mobility. It is estimated that within the US and the EU the prevalence of osteoarthritis is approximately 62 million people. About half of these patients (31 million) experiences pain related to OA (Symptomatic OA). The prevalence of people with symptomatic OA is estimated at 17.9 million (6.1% of the total population) in the US and 13.1 million (4.3%) for the top five largest European markets.[6]

Fig 5:



The prevalence of OA rises with age. In fact – in the US, the over-65 population accounts for more than half of all OA cases. The prevalence of OA rises from 8.4% in patients aged 35-44 to 41.4% for patients above the age of 65.[7] The anticipated growth in the elderly population is anticipated to result in an increased prevalence of OA in the major global markets. The US is expected to have an additional 9 million more people aged 65 and older in 2020 than in 2006.

Osteoarthritis Treatment Paradigm

First-line treatment options for OA (acetaminophen and lifestyle recommendations) are successful to a limited extent. Patients typically shift to either traditional NSAIDs or selective COX-2 inhibitors as second-line therapy. Some patients may progress further and require treatment for flare-ups (corticosteroids, hyaluronic acid) or invasive surgery.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely available for decades. Due to their well-established efficacy and dosing profile, they remain commonly used agents for mild-to-moderate OA. However, they may cause serious GI side effects with long-term use. Long-term use of any of the traditional NSAIDs, may damage the mucous layer of the stomach, resulting in general stomach discomfort or, more seriously bleeding and ulcer formation.

Selective COX-2 inhibitors are a subset of NSAIDs that specifically inhibit the COX-2 enzyme. The intent of this specificity is to reduce GI side effects commonly associated with the traditional NSAIDs. However, the COX-2 class has been associated with a higher incidence of cardiovascular side effects.

Treatment Choices

Physicians make their treatment choice based on four primary factors since comparative studies have found no clear efficacy differences:

- Dosing and Frequency
- Gastrointestinal Risks
- Cardiovascular Risks
- Renal Risks

Physicians must balance the different risks based on individual patient circumstances – but none of the current therapies provide the combination of simplified dosing with minimal GI, cardiovascular and renal risks.[8]

Nimesulide Extended Release tablet is positioned to meet the identified unmet needs with current therapeutics for the treatment of OA. Panacea Biotec's brand Willgo®, based on the present invention (bilayered, controlled release Nimesulide tablets), sold in India, has been proven to be a highly effective product for the management of chronic OA pain and inflammation offering the advantage of once a day dosing with favorable GI tolerability and good safety in Cardio Vascular and Renal parameters. A major challenge that was overcome by the present invention was the development of an extended release

formulation despite the region specific absorption of Nimesulide from the upper parts of GIT. The product was introduced in India as a new drug delivery product supported by promising clinical trial results. The product (marketed under the brand name Willgo®) was able to address a significant unmet medical need which resulted in consistently growing sales. As an example the IMS-ORG audited data for the last three years is presented below:

Table 12: Sales of Willgo® Tablet (Extended Release Nimesulide) and Nimulid® Tablet (Immediate Release Nimesulide) in India

OUR BRANDS	Apr-Dec 06	MAT DEC 07	MAT DEC 08	Apr-Dec 06	MAT DEC 07	MAT DEC 08
	ABS Value	ABS Value	ABS Value	ABS Units	ABS Units	ABS Units
WILLGO TABS	23,555,210	34,804,568	42,599,763	594,829	863,637	995,150
NIMULID TABS	94,715,001	106,154,891	102,530,488	4,079,327	4,313,504	4,168,075

ABS Value means Absolute Amount in Rupees
ABS Units means Absolute Number of Strips of Each Brand (Each Strip contains 10 Tablets)
MAT Means Moving Annual Total
TABS means Tablets

The Table 1 indicates the sales growth of Willgo® Tablet (Extended Release Tablet) and Nimulid® Tablet (Immediate Release Tablet) in absolute value and units for the period i.e. Apr 2006 to Dec 2006, Jan 2007 to Dec 2007 and Jan 2008 to Dec 2008.

Conclusion: It has been concluded from the above table that the sales growth of Willgo® (Extended Release Nimesulide) is increasing year by year. Percentage growth Sales of Willgo® has increased by 80.8% in last two years from Dec 2006 to Dec 2008. While percentage sales growth of Nimulid® Tablet (Immediate Release Nimesulide) has increased only by 8.25 in last two years from Dec 2006 to Dec 2008 and decreased by 3.4 in last one year from Dec 2007 to Dec 2008.